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(21) International Application Number: PCT/GB99/01799 (22) International Filing Date: 2 June 1999 (02.06.99) (30) Priority Data: 9812038.9 4 June 1998 (04.06.98) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BROUGHTON, Howard, Barff [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). BRYANT, Helen, Jane [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CHAMBERS, Mark, Stuart [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CURTIS, Neil, Roy [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: TETRAHYDROINDOLONE DERIVATIVES AS GABAAALPHA5 LIGANDS FOR ENHANCING COGNITION (57) Abstract <p>The present invention provides compounds of formula (I) where A is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, aryl C₁₋₆ alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C₁₋₆ alkyl, CF₃, CN, NO₂ or NH₂, NR¹R¹⁰, S(O)_pR¹, heteroaryl C₁₋₆ alkyl or heteroaryl; B is phenyl or a 5-membered ring, a 6-membered heteroaromatic ring substituted by one or more substituents independently chosen from: cyano; and aryl, aryl C₁₋₆ alkyl or a 5-membered ring; R² and R³ are independently hydrogen or C₁₋₆ alkyl or together with the carbon atom to which they are attached form a C₃₋₈ cycloalkyl group; pharmaceutical compositions comprising them; their use in therapy and in the manufacture of medicaments for enhancing cognition, for example in Alzheimer's Disease, particularly through acting at the GABA_A α5 receptor subunit; and methods of treatment using them.</p>		

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TETRAHYDROINDOLONE DERIVATIVES AS GABAA α 5 LIGANDS FOR ENHANCING COGNITION

The present invention relates to tetrahydroindolone derivatives,
5 pharmaceutical compositions comprising them and to their use in therapy.
More particularly, this invention is concerned with substituted derivatives
which are ligands for GABA $_A$ receptors, in particular for GABA $_A$ α 5
receptors and are therefore useful in therapy particularly where cognition
enhancement is required.

10 Receptors for the major inhibitory neurotransmitter, gamma-
aminobutyric acid (GABA), are divided into two main classes: (1) GABA $_A$
receptors, which are members of the ligand-gated ion channel superfamily;
and (2) GABA $_B$ receptors, which may be members of the G-protein linked
receptor superfamily. Since the first cDNAs encoding individual GABA $_A$
15 receptor subunits were cloned the number of known members of the
mammalian family has grown to thirteen (six α subunits, three β subunits,
three γ subunits and one δ subunit). It may be that further subunits
remain to be discovered; however, none has been reported since 1993.

Although knowledge of the diversity of the GABA $_A$ receptor gene
20 family represents a huge step forward in our understanding of this ligand-
gated ion channel, insight into the extent of subtype diversity is still at an
early stage. It has been indicated that an α subunit, a β subunit and a γ
subunit constitute the minimum requirement for forming a fully
functional GABA $_A$ receptor expressed by transiently transfecting cDNAs
25 into cells. As indicated above, a δ subunit also exists, but is apparently
uncommon in the native receptor.

Studies of receptor size and visualisation by electron microscopy
conclude that, like other members of the ligand-gated ion channel family,
the native GABA $_A$ receptor exists in pentameric form. The selection of at
30 least one α , one β and one γ subunit from a repertoire of thirteen allows for
the possible existence of more than 10,000 pentameric subunit
combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include $\alpha 1\beta 2\gamma 2$,
5 $\alpha 2\beta 2/3\gamma 2$, $\alpha 3\beta 2/3$, $\alpha 2\beta \gamma 1$, $\alpha 5\beta 3\gamma 2/3$, $\alpha 6\beta \gamma 2$, $\alpha 6\beta \delta$ and $\alpha 4\beta \delta$. Subtype assemblies containing an $\alpha 1$ subunit are present in most areas of the brain and account for over 40% of GABA_A receptors in the rat. Subtype assemblies containing $\alpha 2$ and $\alpha 3$ subunits respectively account for about 25% and 17% of GABA_A receptors in the rat. Subtype assemblies
10 containing an $\alpha 5$ subunit are primarily hippocampal and represent about 4% of receptors in the rat.

A characteristic property of some GABA_A receptors is the presence of a number of modulatory sites, of which the most explored is the benzodiazepine (BZ) binding site through which anxiolytic drugs such as
15 diazepam and temazepam exert their effect. Before the cloning of the GABA_A receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a GABA_A receptor comprising the $\alpha 1$
20 subunit in combination with $\beta 2$ and $\gamma 2$. This is the most abundant GABA_A receptor subtype, representing almost half of all GABA_A receptors in the brain.

Two other major populations are the $\alpha 2\beta \gamma 2$ and $\alpha 3\beta \gamma 2/3$ subtypes. Together these constitute approximately a further 35% of the total GABA_A
25 receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha 5$ -containing subtype assemblies. The physiological role of these subtypes has hitherto been unclear because no sufficiently selective agonists or antagonists were
30 known.

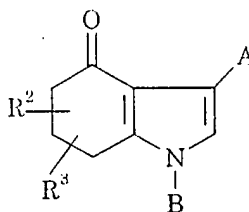
It is now believed that agents acting as BZ agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ or $\alpha 3\beta\gamma 2$ subunits will possess desirable anxiolytic properties. The $\alpha 1$ -selective GABA_A receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the
5 sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through GABA_A receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that GABA_A receptor agonists which bind more effectively to the $\alpha 2$ and/or $\alpha 3$ subunit than to $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause
10 sedation. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

A number of dementing illnesses such as Alzheimer's disease are characterised by a progressive deterioration in cognition in the sufferer. It would clearly be desirable to enhance cognition in subjects desirous of such
15 treatment, for example for subjects suffering from a dementing illness. It is believed this can be done utilising compounds which are ligands for the GABA_A $\alpha 5$ receptor subtype.

WO-A-9616954 mentions three thienylcyclohexanone derivatives substituted by substituted arylaminocarbonyl on the thiophene ring as
20 fungicides.

Van Rhee *et al*, *J. Med. Chem.*, 1996, **39**, 398-406 discloses related compounds as adenosine receptor antagonists which differ in having an ester group on the thiophene ring.

The present invention provides a compound of formula (I) or a
25 pharmaceutically acceptable salt thereof:



(I)

where A is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, arylC₁₋₆alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C₁₋₆alkyl, CF₃, CN, NO₂ or NH₂, NR¹R¹⁰, S(O)_pR¹, heteroarylC₁₋₆alkyl or heteroaryl where heteroaryl is a 5- or 6-membered heteroaromatic ring as defined for B below;

B is phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, a 6-membered heteroaromatic ring containing 1, 2, 3 or 4 nitrogen atoms, each of which rings is optionally substituted by one or more substituents independently chosen from: cyano; C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_rR⁴; COR⁵; and aryl, arylC₁₋₆alkyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N wherein the aryl ring or 5-membered ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

R¹ is hydrogen; C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl or C₃₋₆cycloalkenyl each of which is optionally substituted by amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkoxy, C₁₋₆alkylaminocarbonyl, one, two or three hydroxy groups, one, two or three halogen atoms or a four, five or six-membered saturated heterocyclic ring containing a nitrogen atom and optionally either an oxygen atom or a further nitrogen atom which ring is optionally substituted by C₁₋₆alkyl on the further

nitrogen atom; aryl, arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl
optionally substituted on the aryl ring by halogen, nitro, cyano,
C₁₋₆alkylcarbonylamino, hydroxy or C₁₋₆alkoxy; or a five-membered
aromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S
5 provided that not more than one heteroatom is other than N, or a six-
membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring
is optionally substituted by halogen, C₁₋₆alkoxy, C₁₋₆alkylthio, aryl,
C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

R² and R³ are independently hydrogen or C₁₋₆alkyl or together with
10 the carbon atom to which they are attached form a C₃₋₈ cycloalkyl group;

~~R⁴ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl or~~
CH₂(CO)_mNR⁸R⁹;

R⁵ is NR⁶R⁷, C₁₋₆alkyl or C₁₋₆alkoxy;

R⁶ is independently as defined for R⁴;

15 R⁷ is aryl optionally substituted by halogen, nitro or cyano;

R⁸ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl,
C₂₋₆alkenyl, C₂₋₆alkynyl; arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl
optionally substituted on the aryl ring by halogen, nitro or cyano;
thiophene or pyridine;

20 R⁹ is C₁₋₆alkyl; C₂₋₆alkenyl; C₂₋₆alkynyl; or phenyl optionally
substituted by one, two or three substituents independently chosen from
halogen, CF₃, OCH₃, nitro and cyano;

R¹⁰ is hydrogen or C₁₋₆ alkyl;

R¹⁴ is hydrogen or C₁₋₆alkyl;

25 m is zero or 1;

p is zero, 1 or 2;

q is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2; and

30 t is 0, 1 or 2.

B may be phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from: C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_rR⁴; COR⁵; and aryl or arylC₁₋₆alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

B is preferably an optionally substituted phenyl or optionally substituted 6-membered heteroaromatic ring. The optional substituents are preferably one or two groups independently chosen from halogen, C₁₋₆alkyl, trifluoromethyl, cyano and an unsubstituted 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N. The optional substituent is preferably chosen from halogen, C₁₋₆alkyl, trifluoromethyl and cyano.

B is most particularly optionally substituted phenyl or pyridine. In particular B may be pyridine and preferably pyridin-2-yl.

Thus when B is a heteroaromatic ring it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine which is unsubstituted or substituted by C₁₋₆alkyl, halogen, SR⁴, COR⁵ or benzyl optionally substituted by halogen. When B is a 5- or 6-membered ring having one unsaturation it is preferably oxazolidinyl or imidazolinyl optionally substituted by halogen or C₁₋₄alkyl.

Particular embodiments of B are (1-phenylsulphonyl)pyrazol-3-yl, 1-acetylpyrazol-3-yl, (3-ethoxycarbonyl)isoxazol-5-yl, (3-isopropyl)-1,2,4-oxadiazol-5-yl, imidazolin-2-yl, pyrazol-4-yl, 2-methyl-1,3,4-oxadiazol-5-yl, oxazolidin-2-yl, 2-methyltetrazol-5-yl, pyrazol-3-yl, 2-propyltetrazol-5-yl, thiazol-2-yl, 4-methyl-1,2,4-triazol-3-yl, (4-ethoxycarbonyl)thiazol-2-yl, (4-

trifluoromethyl)thiazol-2-yl, (4-acetyl)thiazol-2-yl, (4-methyl)thiazol-2-yl, pyrrol-2-yl, pyrid-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 4-benzyl-1,2,4-triazol-3-yl, 1-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, pyrazin-2-yl, pyrimidin-5-yl, 3-(N-methylaminocarbonyl)thiazol-2-yl, thiazol-5-yl, isoxazol-5-yl, pyrid-3-yl, pyrid-4-yl, 1,3,4-oxadiazol-5-yl and 1-methylsulphonylpyrazol-3-yl.

Other particular embodiments of B are pyridin-2-yl, 6-methyl pyridin-2-yl, thiazol-2-yl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 4-methylphenyl, 3-methylphenyl, pyrimidin-2-yl, pyridin-3-yl, 2-cyanophenyl, 5-chloropyridin-2-yl and 6-(thiazol-2-yl) pyridin-2-yl.

~~R¹ is preferably C₁₋₆alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl each of which is optionally substituted by amino, di(C₁₋₆alkyl)amino, hydroxy, C₁₋₆alkoxy, C₁₋₆alkylaminocarbonyl or one, two or three halogen atoms; aryl or arylC₁₋₆alkyl optionally substituted on the aryl ring by halogen, C₁₋₆alkylcarbonylamino or C₁₋₆alkoxy; or a five-membered aromatic ring containing 1, 2 or 3 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, or a six-membered aromatic ring containing 1 or 2 nitrogen atoms, which ring is optionally substituted by halogen, C₁₋₆alkoxy, C₁₋₆alkylthio, aryl or C₁₋₆alkyl.~~

More preferably R¹ is C₁₋₆alkyl, C₁₋₄alkenyl, or C₃₋₆cycloalkyl each of which is optionally substituted by di(C₁₋₄alkyl)amino, C₁₋₄alkoxy, C₁₋₄alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenyl or phenylC₁₋₄alkyl optionally substituted on the phenyl ring by chlorine, fluorine, C₁₋₄alkoxy or C₁₋₄alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C₁₋₄alkyl, phenyl, fluorine or C₁₋₄alkylthio. In particular R¹ is C₁₋₆alkyl, phenyl, benzyl or pyridyl.

A may be C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, arylC₁₋₆alkyl, aryl, S(O)_pR¹, heteroarylC₁₋₆alkyl or heteroaryl where heteroaryl is a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that

not more than one heteroatom is other than N, or a 6-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by one or more substituents independently chosen from:

- 5 C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_rR⁴; COR⁵; and aryl or aryl C₁₋₆alkyl wherein the aryl ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen.

- 10 When A is not S(O)_pR¹ it is preferably C₁₋₆alkyl, C₂₋₆alkenyl or C₃₋₆cycloalkyl. A may be C₁₋₆alkyl such as ethyl.

A is preferably C₁₋₆alkyl, C₂₋₆alkenyl, arylC₁₋₆alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C₁₋₆alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C₁₋₆alkyl, NHR¹ or SR¹.

- 15 Particular embodiments of A include ethyl, 1,1-dimethylethyl, cyclopropyl, thiazol-2-yl, ethylthio, benzyl, phenyl, methylthio, ethenyl, phenylamino, pyridin-2-ylamino, phenylthio, pyrid-2-yl, benzylthio, oxazol-2-yl, 3-methyl-1,2,4-oxadiazol-5-yl, thiazol-5-yl, 4-chlorophenyl, 4-methylthiazol-2-yl, 3-chlorophenyl and 2-chlorophenyl.

- 20 Particular embodiments of A are phenyl, cyclohexyl, 2-methylprop-1-enyl, methylthio, ethyl, isopropyl, propyl, cyclobutyl, but-3-enyl, cyclopropyl, methanesulphonyl, methyl, benzyl, methanesulphinyl, (1,1-dimethylethyl)thio, pentylthio, (4-methyl-1,2,4-triazol-3-yl)thio, hexylthio, benzylamino, (3-imidazol-1-ylpropyl)amino, (pyrid-2-yl)amino, 2-methylprop-1-yl, [3-(4-methylpiperazin-1-yl)propyl]amino, methylamino, 25 (2-hydroxyethyl)amino, azetidin-1-yl, tert-butylamino, isopropylthio, (2-hydroxyethyl)thio, methoxy, dimethylamino, cyclobutoxy, phenoxy, butylthio, (3-chloropropyl)thio, (2-phenylethyl)thio, propylthio, (2-methylbutyl)thio, (2,2,2-trifluoroethyl)thio, (1-methylpropyl)thio, 30 (4-chlorophenyl)thio, (3-fluorophenyl)thio, (4-acetylamino)phenylthio, (4-methoxyphenyl)thio, (1-methylimidazol-2-yl)thio, (thiophen-2-yl)thio,

(imidazol-2-yl)thio, (4-phenylthiazol-2-yl)thio, (1,2,4-triazol-3-yl)thio, (5-methyl-1,3,4-thiadiazol-2-yl)thio, (5-methylthio-1,3,4-thiadiazol-2-yl)thio, benzylthio, cyclopentylthio, (2-methylpropyl)thio, (furan-2-ylmethyl)thio, (2-hydroxy-1-methylpropyl)thio, (2,3-dihydroxypropyl)thio, (2-hydroxypropyl)thio, ((N-methylaminocarbonyl)methyl)thio, (pyrid-4-yl)thio, (pyrimidin-2-yl)thio, (thiazol-2-yl)thio, prop-2-enylthio, (pyrid-2-yl)thio, ethylthio, phenylthio, (N,N-dimethyl-2-aminoethyl)thio, (2-methoxyethyl)thio, (furan-2-ylmethyl)amino, (2-methylpropyl)amino, propylamino, (2-methoxyethyl)amino, cyclopropylamino, isopropylamino, ethylamino, cyclobutylamino and isopropoxy.

When A is heteroaryl it may be a thiazole, pyrazole, pyrimidine, tetrazole, triazole, oxadiazole, oxazole, pyridine, imidazole or pyrazine.

R² and R³ are preferably independently chosen from hydrogen, methyl and propyl or are attached to the same carbon atom and together with that atom form a C₃₋₆cycloalkyl group. Alternatively R² and R³ are independently chosen from hydrogen and methyl. R² may be hydrogen with R³ being hydrogen, methyl or isopropyl. Preferably both are methyl. Preferably R² and R³ are geminal to each other, preferably at the 6-position, i.e. beta to the carbonyl group in formula I.

R⁴ may be hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, aryl or CH₂(CO)_mNR⁸R⁹. R⁴ is preferably hydrogen, C₁₋₄alkyl or CH₂(CO)_mNR⁸R⁹, more preferably hydrogen, methyl or CH₂CONR⁸R⁹ and most preferably methyl or CH₂CONR⁸R⁹.

R⁵ is preferably methyl, methoxy, ethoxy or NR⁶R⁷ and most preferably methyl, ethoxy or NR⁶R⁷.

R⁶ may be hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, aryl or CH₂(CO)_mNR⁸R⁹. R⁶ is preferably hydrogen or C₁₋₄alkyl and most preferably hydrogen.

R⁷ is preferably phenyl unsubstituted or substituted by halogen, nitro or cyano, more preferably optionally substituted by halogen, such as chlorine.

R⁸ is preferably hydrogen or C₁₋₆alkyl and most preferably
5 hydrogen.

R⁹ is preferably C₁₋₆alkyl or phenyl unsubstituted or substituted by one, two or three substituents independently chosen from halogen, nitro and cyano, more preferably C₁₋₆alkyl or phenyl optionally substituted by one or two substituents independently chosen from halogen and nitro and
10 most preferably *tert*-butyl or phenyl optionally substituted with one or two substituents chosen from chlorine and nitro, such as 4-chlorophenyl.

R¹⁰ is preferably hydrogen or methyl, particularly hydrogen.

R¹⁴ is generally hydrogen or C₁₋₄alkyl and most preferably hydrogen.
m is preferably 1.

15 p is preferably zero or two, most preferably zero.

q is preferably 1.

r is preferably 1.

s is preferably 0 or 1. s may be 1. s may be 0

t is preferably 0 or 1. t may be 1. t may be 0.

20 A specific Example of a compound according to the present invention is:

6,6-dimethyl 3-ethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one
and the pharmaceutically acceptable salts thereof.

Further specific Examples of compounds according to the present
25 invention are:

6,6-dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-
tetrahydroindol-4-one;

3-cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

3-ethyl-6,6-dimethyl-1-(pyrimidin-2-yl)-4,5,6,7-tetrahydroindol-4-one;

30 6,6-dimethyl-3-ethyl-1-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;

6,6-dimethyl-3-ethyl-1-(3-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one;

- 6,6-dimethyl-3-ethyl-1-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-ethyl-1-(4-methylphenyl)-4,5,6,7-tetrahydroindol-4-one;
- 1-(4-chlorophenyl)-6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydroindol-4-one;
- 5 6,6-dimethyl-3-ethyl-1-(4-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-ethyl-1-(3-methylphenyl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-
- 10 tetrahydroindol-4-one;
-
- 6,6-dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-phenyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-
- 15 one;
- 6,6-dimethyl-1-(pyridin-2-yl)-3-vinyl-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-phenylmethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-
- one;
- 6,6-dimethyl-3-(oxazol-2-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-
- 20 one;
- 6,6-dimethyl-1-(pyridin-2-yl)-3-(thiazol-5-yl)-4,5,6,7-tetrahydroindol-4-
- one;
- 6,6-dimethyl-3-phenylamino-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-
- one;
- 25 6,6-dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-ylamino)-4,5,6,7-
- tetrahydroindol-4-one;
- 6,6-dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-
- one;
- 6,6-dimethyl-3-(4-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-
- 30 tetrahydroindol-4-one;

- 3-(4-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 3-(3-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 5 3-(2-chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 1-(5-chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 10 6,6-dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 1-(2-cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 15 and the pharmaceutically acceptable salts thereof.
- Further specific compounds of the present invention are:
- 6,6-dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6,6-dimethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 20 6,6-dimethyl-3-(3-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 3-(1,1-dimethylethyl)-6-methyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 25 3-ethyl-6-methyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 6-methyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 3-(1,1-dimethylethyl)-6-(2-methylethyl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one;
- 30 and the pharmaceutically acceptable salts thereof.

There is also provided a pharmaceutical composition comprising a compound of formula I according to the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

5 Preferably the compositions according to the present invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, by inhalation or insufflation or administration by transdermal patches or by buccal cavity absorption wafers.

10 For preparing solid compositions such as tablets, the principal ~~active ingredient is mixed with a pharmaceutical carrier, e.g. conventional~~ tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation
15 composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into
20 equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a
25 dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to
30 pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials

including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection
5 include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as
10 tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may
15 contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the
20 nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

25 Compositions of the present invention may also be presented for administration in the form of trans-dermal patches using conventional technology. The compositions may also be administered via the buccal cavity using, for example, absorption wafers.

In disorders associated with GABA_A α receptors, a suitable dosage
30 level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100

mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The present invention also provides a process for the preparation of a pharmaceutical composition which comprises adding a compound of
5 formula (I) or a pharmaceutically acceptable salt thereof to a pharmaceutically acceptable excipient.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human or animal body, in particular for the treatment or prevention
10 of conditions for which the administration of a cognition enhancing agent is desirable, such as Alzheimer's disease.

The compounds of formula (I) are of potential value in the treatment or prevention of a wide variety of clinical conditions which can be alleviated by a ligand selective for GABA_A receptors containing the $\alpha 5$
15 subunit. In particular, they are desirably inverse agonists of the $\alpha 5$ subunit.

Thus, for example, such a ligand can be used in a variety of disorders of the central nervous system. Such disorders include delirium, dementia and amnesic and other cognitive disorders. Examples of
20 delirium are delirium due to substance intoxication or substance withdrawal, delirium due to multiple etiologies and delirium NOS (not otherwise specified). Examples of dementia are: dementia of the Alzheimer's type with early onset which can be uncomplicated or with delirium, delusions or depressed mood; dementia of the Alzheimer's type,
25 with late onset, which can be uncomplicated or with delirium, delusions or depressed mood; vascular dementia which can be uncomplicated or with delirium, delusions or depressed mood; dementia due to HIV disease; dementia due to head trauma; dementia due to Parkinson's disease;
30 dementia due to Huntington's disease; dementia due to Pick's disease; dementia due to Creutzfeld-Jakob disease; dementia which is substance-induced persisting or due to multiple etiologies; and dementia NOS.

Examples of amnestic disorders are amnestic disorder due to a particular medical condition or which is substance-induced persisting or which is amnestic disorder NOS. In particular the compounds of formula (I) may be of use in conditions which require cognition enhancement.

5 Where the compounds of the present invention are selective ligands for GABA_A α 2 or α 3 subtype receptors they may be used in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder,
10 animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; and depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder,
15 bipolar I and bipolar II manic disorders, and cyclothymic disorder.

 The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a condition requiring the administration of a ligand selective for GABA_A
20 receptors containing the α 5 subunit, in particular for conditions requiring cognition enhancement such as Alzheimer's disease. Other conditions to be treated include cognition deficits due to traumatic injury, stroke, Parkinson's disease, Downs syndrome, age related memory deficits, attention deficit disorder and the like.

25 There is also disclosed a method of treatment or prevention of a condition associated with GABA_A receptors containing the α 5 subunit in a subject suffering from or prone to such a condition which comprises administering to that subject a therapeutically or prophylactically effective amount of a compound of formula (I) or a pharmaceutically
30 acceptable salt thereof. In particular there is disclosed the treatment and

prevention of conditions which require the administration of a cognition enhancing agent, such as Alzheimer's disease.

As used herein, the expression "C₁₋₆alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C₂₋₆alkenyl", "C₂₋₆alkynyl", "C₁₋₆alkenyl", "C₂₋₄alkenyl" and "C₂₋₄alkynyl" are to be construed in an analogous manner.

The expression "C₃₋₆cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. "C₅₋₆cycloalkenyl", "C₃₋₈cycloalkyl" and "C₅₋₇cycloalkyl" are to be construed analogously.

Suitable 5- and 6-membered heteroaromatic rings include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, isothiazolyl, imidazolyl, tetrazolyl, oxadiazolyl and thiadiazolyl groups. These rings also include thiazolyl and triazolyl groups.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine, chlorine and bromine.

The expression "arylC₁₋₆alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl. "ArylC₂₋₆alkenyl", "arylC₂₋₆alkynyl" and "heteroarylC₁₋₆alkyl" should be construed in an analogous fashion.

Typical aryl groups include phenyl and naphthyl. Preferably the aryl is phenyl.

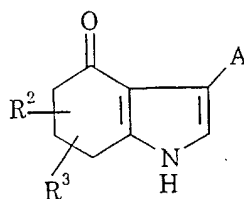
For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable

acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include
5 alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds of formula (I) have at least one asymmetric
10 centre, they may accordingly exist as enantiomers. Where the compounds of formula (I) possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

15 The present invention also provides a process for producing a compound of formula I which comprises reacting a compound of formula II with a compound of formula III:



(II)

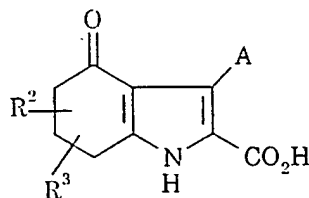
Hal-B

(III)

20

wherein R², R³, A and B are as defined above and Hal is a halogen atom such as bromine, chlorine or fluorine, generally in a solvent such as DMF and in the presence of a strong base such as NaH, generally with heating to about 90°C for about 6 h. Alternatively the reaction may be carried out
25 using CuBr in DMF in the presence of K₂CO₃ generally with heating to about 180°C for about 48h.

The compound of formula II is prepared by decarboxylating a compound of formula IV:

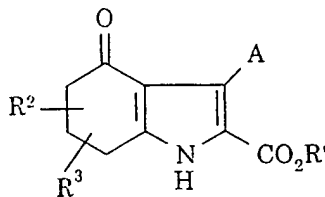


(IV)

5

wherein R² and R³ are as defined above by heating at about 100°C for about 45 minutes generally in the presence of an acid such as acetic acid and/or hydrochloric acid.

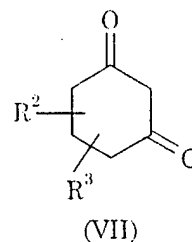
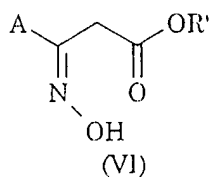
The compounds of formula IV is prepared by hydrolysing a
10 compound of formula V:



(V)

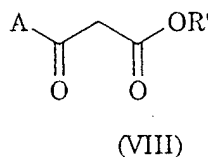
wherein R² and R³ are as defined above generally by heating at
15 reflux for about 6h generally in the presence of a base such as KOH and a solvent such as ethanol and water. This reaction can also be performed by heating the compound of formula V in DMSO and H₂O at about 150°C for about 18h.

The compound of formula V is prepared by reacting a compound of
20 formula VI with a compound formula VII:



wherein A and R¹ are defined above, generally with heating to about 100°C for about 1h in a buffered solution such as acetic acid/sodium acetate in the presence of a catalyst such as zinc optionally in powdered form. This reaction can produce a compound of formula II directly when it is carried out at about 150°C.

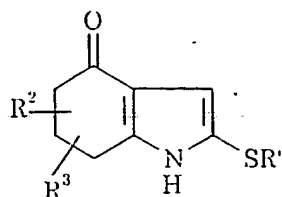
The compound of formula VI is prepared by reacting a compound of formula VIII:



wherein A and R' are as defined above, with sodium nitrite generally in the presence of an acid such as acetic acid in a solvent such as water at room temperature for about 1h.

The compounds of formulae III, VII and VIII are either commercially available or can be made by the skilled person from commercially available compounds by known methods.

In an alternative process, a compound of formula II in which A is SR¹, wherein R¹ is as defined above, is prepared by reacting a compound of formula IX:

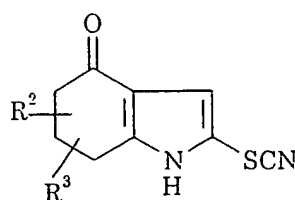


(IX)

wherein R² and R³ are as defined above, with heating for about four hours
in the presence of an acid such as trifluoroacetic acid, generally in a
5 solvent such as ClCH₂CH₂Cl. The resulting product is a mixture of
compounds of formulae II and IX which are then separated by
conventional means.

The compound of formula IX is prepared by reacting a compound of
formula X:

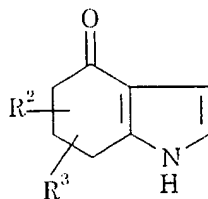
10



(X)

wherein R² and R³ are as defined above, with R¹I, wherein R¹ is as defined
15 above, in the presence of a solvent such as methanol with a base as ROH
for about 3h at room temperature. The compound R¹I is commercially
available or may be made by methods known to the skilled person from
commercially available compounds.

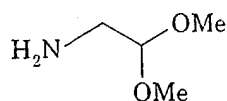
The compound of formula X is made by reacting a compound of
20 formula XI:



(XI)

wherein R² and R³ are as defined above, with bromine and KSCN in a solvent such as methanol at a temperature of from - 30°C to room temperature.

The compound of formula XI can be made by reacting a compound of formula VII with a compound of formula XII:



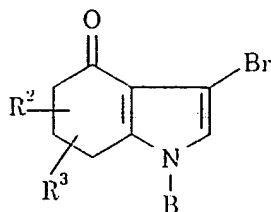
(XII)

with paratoluensulphonic acid generally in a solvent such as toluene with heating for about 3 h, and then carrying out a Michael addition by heating at about 40°C for about 9 h with an acid such as HCl, preferably at 3N.

The compound of formula XII is commercially available or can be made by known methods from commercially available compounds.

Alternatively the compound of formula XI may be obtained commercially.

Alternatively a compound of formula I is produced by reacting a compound of formula XIII with a compound of formula XIV:



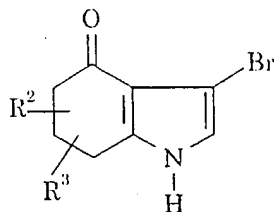
Z - A

(XIII)

(XIV)

wherein R^2 , R^3 , A and B are as defined above:

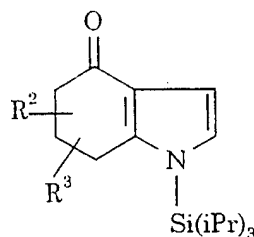
- (i) where Z is $\text{Sn}(\text{Bu})_3$ in the presence of
 5 tetrakis(triphenylphosphene) palladium or
 dichlorobis(triphenylphosphine) palladium in a solvent such as dioxan
 generally with heating to reflux in a solvent such as dioxan or
 hexamethylphosphoramide for about 24h to 48h at about 70°C ;
- (ii) where Z is $\text{B}(\text{OH})_2$ in the presence of
 10 tetrakis(triphenylphosphene) palladium generally in a biphasic mixture of
 solvents such as ethylene glycol dimethyl ether and water and in the
 presence of a mild base such as Cs_2CO_3 or Na_2CO_3 at reflux for about 8h;
 or in the presence of $\text{Cu}(\text{OAc})_2$ in a solvent such as DCM, in the presence of
 a base such as Et_3N generally at room temperature;
- 15 (iii) where Z is NR^{10}H in the presence of
 tris(dibenzylideneacetone)dipalladium generally with a base such as
 NaO^tBu , a solvent such as toluene and a compound such as (R)-(+)-2,2'-
 bis(diphenylphosphino)-1,1'-binaphthyl generally at reflux for about 3h.
 (This last method produces compounds of formula I in which A is NR^1R^{10}).
- 20 The compound of formula XIII can be produced by reacting a
 compound of formula XV:



(XV)

wherein R^2 and R^3 are as defined above with a compound of formula III as defined above generally in the presence of a strong base such as NaH and in a solvent such as DMF for about 5 min.

- 5 The compound of formula XV can be produced by reacting a compound of formula XVI:



(XVI)

- wherein R^2 and R^3 are as defined above with a brominating agent such as N-bromosuccinimide generally in a solvent such as THF generally with
10 cooling to about -78°C for about 1h.

The compound of formula XVI can be produced by reacting a compound of formula XI as defined above with $(i\text{Pr})_3\text{SiCl}$ generally in a solvent such as DMF at about 0°C for about 1h.

- Compounds of formula XIV are commercially available or can be
15 made by known by methods from commercially available compounds.

A compound of formula I may also be prepared by interconversion from another compound of formula I by known methods.

- Compounds of formula I in which A is $\text{S}(\text{O})_p\text{R}^1$ wherein p is one or two can be obtained by reacting a compound of formula I in which A is
20 $\text{S}(\text{O})_p\text{R}^1$ in which p is zero or one and R^1 is as defined above with a

stoichiometric quantity of mCPBA, generally in a solvent such as CH₂Cl₂: dioxan with cooling to about -78°C.

It will be understood that the above transformations of S(O)_pR¹ are illustrative and other standard techniques known to the skilled person
5 may alternatively be used.

The following Examples illustrate pharmaceutical compositions according to the invention.

COMPOSITION EXAMPLE 1A Tablets containing 1-25mg of
10 compound

		<u>Amount mg</u>		
15	Active Ingredients(s)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
	Magnesium Stearate	0.5	0.5	0.5

COMPOSITION EXAMPLE 1B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Active Ingredients(s)	26.0	50.0	100.0
5	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5

- 10 The active ingredient(s), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg,
- 15 50.0mg and 100mg of the active compound per tablet.

COMPOSITION EXAMPLE 2 Parenteral injection

		<u>Amount</u>
	Active Ingredient(s)	1 to 100mg
20	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
	Water for injection	to 10ml

- 25 The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredient(s) is (are) dissolved or suspended in the solution and made up to volume.

COMPOSITION EXAMPLE 3 Topical formulation

	<u>Amount</u>
Active Ingredient(s)	1-10g
Emulsifying Wax	30g
5 Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The
10 active ingredient(s) is (are) added and stirring continued until dispersed.
The mixture is then cooled until solid.

The following Examples illustrate the compounds of the present invention.

The compounds in accordance with this invention potentially inhibit
15 the binding of [³H]-flumazenil to the benzodiazepine binding site of human GABA_A receptors containing the $\alpha 5$ subunit stably expressed in Ltk⁻ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH₂PO₄, 100 mM KCl, pH 7.4 at room temperature.
- 20 • [³H]-Flumazenil (18 nM for $\alpha 1\beta 3\gamma 2$ cells; 18 nM for $\alpha 2\beta 3\gamma 2$ cells; 10 nM for $\alpha 3\beta 3\gamma 2$ cells; 10 nM for $\alpha 5\beta 3\gamma 2$ cells) in assay buffer.
- Flunitrazepam 100 μ M in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

25 Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets
30 are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 μ l of assay buffer.
- 50 μ l of [3 H]-flumazenil (final concentration for $\alpha 1\beta 3\gamma 2$: 1.8 nM; for $\alpha 2\beta 3\gamma 2$: 1.8 nM; for $\alpha 3\beta 3\gamma 2$: 1.0 nM; for $\alpha 5\beta 3\gamma 2$: 1.0 nM).
- 50 μ l of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 μ M final concentration.
- 100 μ l of cells.

10 Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if
15 using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillate. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

20 The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [3 H]Ro 15-1788 from the $\alpha 5$ subunit of the human GABA_A receptor of 500 nM or less, preferably of 100 nM or less, and more particularly of 50 nM or less.

25 More preferably the compounds of the present invention are inverse agonists at the GABA_A $\alpha 5$ subtype whilst being substantially antagonists at the $\alpha 1$, $\alpha 2$ and $\alpha 3$ subtypes. Details of how the effects at the various subtypes can be measured are given in WO-A-9625948.

30 Further, the present compounds preferably bind preferentially to the GABA_A $\alpha 5$ subtype when compared with the $\alpha 1$, $\alpha 2$ and $\alpha 3$ subtypes.

The preferential binding is preferably 5-fold, more preferably 10-fold and most preferably 20-fold.

Intermediate 1

5 6,6-Dimethyl 3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one

Step 1: Ethyl 6,6-dimethyl 3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

10 Ethyl propionylacetate (15g, 0.1mol) and acetic acid (40mL) were cooled to 10°C, and a solution of sodium nitrite (10.4g, 0.15mol) in water (40mL) was added dropwise to the stirred mixture maintaining the temperature below 20°C. After addition the mixture was warmed to room temperature and stirred for 1h. The mixture was then extracted
15 with CH₂Cl₂ (3 x 100mL) and washed with water (100mL), NaHCO₃ (10% (w/v), 100mL) and water (100mL). The organic layer was separated dried (MgSO₄) and evaporated to afford the oxime (13.2g, 73%) as a yellow oil which solidified on standing. The oxime was used without further purification. ¹H NMR (360MHz, d₆-DMSO) δ 1.01
20 (3H,t,J=7.3Hz), 1.23 (3H,t,J=7.1Hz), 2.80 (2H,q,J=7.3Hz), 4.24 (2H,q,J=7.1Hz), 13.16 (1H,br s).

Sodium acetate trihydrate (7.8g, 0.057 mol) and 5,5-dimethyl-1,3-cyclohexandione (10.7g, 0.076mol) in acetic acid (90mL) were heated to 70°C. A solution of the oxime (13.2g, 0.076mol) in acetic acid (45mL)
25 was added portionwise whilst simultaneously adding zinc dust (8g), over a period of 30 min, maintaining the temperature between 70-80°C. The solution was then heated at 100°C for 1h, cooled to 70°C, then water (20mL) was added and heating continued at 100°C for 6h. The solution was then cooled to room temperature, poured into ice-water (400mL) and
30 extracted with CH₂Cl₂ (3 x 200mL). The combined organic layers were washed with water (200mL), separated, dried (MgSO₄) and evaporated.

The residue was chromatographed on silica gel (hexane:EtOAc 4:1→1:1) and the fractions containing the desired product were combined and evaporated. The resultant orange solid was recrystallized from MeOH (30ml) to afford the pyrrole (5.7g, 28%) as a yellow solid. mp 163-166°C.

5 ¹H NMR (360MHz, d₆-DMSO) δ 1.00 (6H,s), 1.06 (3H,t,J=7.3Hz), 1.29 (3H,t,J=7.1Hz), 2.23 (2H,s), 2.64 (2H,s), 2.98 (2H,q,J=7.3Hz), 4.25 (2H,q,J=7.1Hz), 11.86 (1H,s). MS(ES⁺) 264 (M+1).
C₁₅H₂₁NO₃ requires: C, 68.42; H, 8.04; N, 5.32%. Found: C, 68.55; H, 8.12; N, 5.27%.

10

Step 2: 6,6-Dimethyl 3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid

A solution of ethyl 6,6-dimethyl-3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (5.4g, 0.02mol) and KOH (2.9g, 0.05mol) in EtOH (25mL) and water (7.5mL) was heated at reflux for 6h. The mixture was cooled to 60°C, and neutralized by the addition of acetic acid. Water (80mL) was added and the cream precipitate collected by filtration. The precipitate was washed with EtOH and hexane then dried under
15 vacuum at 50°C. The acid (4g, 83%) was isolated as a cream solid, and used without further purification. mp > 198°C. ¹H NMR (360MHz, d₆-DMSO) δ 1.00 (6H,s), 1.04 (3H,t,J=7.3Hz), 2.22 (2H,s), 2.62 (2H,s), 2.98 (2H,q,J=7.3Hz), 11.72 (1H, br s).

20 C₁₃H₁₇NO₃ · 0.4(H₂O) requires: C, 64.39; H, 7.40; N, 5.73%. Found: C, 64.38, H, 7.30; N, 5.70%. MS(ES⁺) 236 (M+1).
25

Step 3: 6,6-Dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A suspension of 6,6-dimethyl-3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid (2.5g, 0.011mol) in acetic acid (12mL) and hydrochloric acid (10M; 0.64mL) was heated at 100°C for 45 min. After this time water (50mL) was added, the cooling bath removed and the solution stirred at room temperature for 2h. The precipitate was collected by filtration and the title pyrrole (1.76g, 87%) isolated as a colourless solid. mp. 150°C-152°C. C₁₂H₁₇NO requires: C, 75.35; H, 8.96; N, 7.32%.

Found: C, 75.00; H, 8.88; N, 7.24%. ¹H NMR (250MHz, CDCl₃) δ 1.10 (6H,s), 1.19 (3H,t,J=7.4Hz), 2.32 (2H,s), 2.63 (2H,s), 2.75 (2H,d of q,J=7.4 and 1.0Hz), 6.42 (1H,br s), 8.00 (1H,br s). MS (ES⁺) 192 (M+1).

Example 1

6,6-Dimethyl 3-Ethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

To a solution of 6,6-dimethyl 3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one (50mg, 0.26mmol) in DMF (4mL) at 0°C, was added NaH (11mg of a 60% dispersion in mineral oil, 0.29mmol). The cooling bath was removed and the mixture stirred at room temperature for 20 min. After this time 2-fluoropyridine (26μl, 0.29mmol) was added and the residue heated at 90°C for 6h. The solvent was evaporated and the residue partitioned between EtOAc (20mL) and water (20mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with hexane:EtOAc (2:1), to give the title pyrrole (18mg, 26%) as a colourless solid. mp 125-127°C ¹H NMR (360MHz, CDCl₃) δ 1.10 (6H,s), 1.23 (3H,t,J=7.4Hz), 2.38 (2H,s), 2.83 (2H,d of q, J=7.4 and 1.0Hz), 2.92 (2H,s), 6.88 (1H,s), 7.25-7.27 (1H,m), 7.30 (1H,d,J=8.0Hz), 7.82 (1H,d of t, J=7.7 and 1.9Hz), 8.51 - 8.57 (1H,m). MS (ES⁺) 269 (M+1).

Example 26,6-Dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-5 tetrahydroindol-4-oneStep 1: 6,6-Dimethyl-3-(1,1-dimethylethyl)-4,5,6,7-tetrahydro-1H-indol-
4-one

- 10 Methyl 4,4-dimethyl-3-oxopentanoate (20g, 0.13mol) and AcOH (48mL) were cooled to 10°C and a solution of NaNO₂ (12.3g, 0.19mol) in water (48mL) was added dropwise to the stirred mixture, maintaining the temperature below 20°C. After addition the mixture was warmed to room temperature and stirred for 2h. The mixture was then extracted
- 15 with DCM (3x100mL). The combined organic layers were evaporated and the residue taken up in ether. The ethereal layer was washed with water (100mL), separated and dried (Na₂SO₄). The resultant yellow gum (22.7g, 96%) was used without further purification. ¹H NMR (250MHz, CDCl₃) δ 1.23 (9H,s), 3.89 (3H,s), 9.00 – 10.00 (1H,br s).
- 20 Sodium acetate trihydrate (20.6g, 0.15mol) and 5,5-dimethyl-1,3-cyclohexandione (16.9g, 0.12mol) in propionic acid (140mL) were heated to 150°C. A solution of the oxime (22.7g, 0.12mol) in propionic acid (70mL) was added via a dropping funnel, whilst simultaneously adding zinc dust (12g) over 20 min. The solution was heated at reflux for 24h
- 25 after which time it was poured into water. The resultant solid was collected by filtration then triturated with ether. The colourless solid (3.7g, 14%) was collected by filtration. ¹H NMR (360MHz, CDCl₃) δ 1.10 (6H,s), 1.35 (9H,s), 2.35 (2H,s), 2.64 (2H,s), 6.43 (1H,d,J=2.2Hz), 7.80 – 8.14 (1H,br s). MS (ES⁺) 220 (M+1).

Step 2: 6,6-Dimethyl-3-(1,1-dimethylethyl)-1-(pyridin-2-yl)-4,5,6,7-1H-tetrahydroindol-4-one

In the same was as described in Example 1 using 6,6-dimethyl-3-(1,1-dimethylethyl)-4,5,6,7-1H-tetrahydroindol-4-one the title compound (24mg, 35%) was isolated as a colourless solid. mp 143-145°C. ¹H NMR (360MHz, CDCl₃) δ 1.08 (6H,s), 1.39 (9H,s), 2.40 (2H,s), 2.89 (2H,s), 6.87 (1H,s), 7.25 – 7.32 (2H,m), 7.83 (1H,d of t, J=7.8 and 2.0 Hz), 8.54 – 8.60 (1H,m). MS (ES⁺) 297 (M+1).

10

Example 3

3-Cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

15 Step 1: Methyl 3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

Methyl 4-cyclopropyl-3-oxobutanoate (15g, 0.106mol) in AcOH (40mL) was cooled to 10°C and a solution of NaNO₂ (9.9g, 0.14mol) in water (40mL) was added dropwise, maintaining the temperature below 20°C. After addition the mixture was warmed to 20°C, stirred for 90 min then washed with DCM (3x100mL). The aqueous phase was separated, evaporated and the residue triturated with ether. The resultant solid was filtered off and the filtrate evaporated to afford a yellow oil. The oil was dissolved in ether, washed with water (100mL) then the organic layer dried (MgSO₄) and evaporated. The oxime (18g, 100%) was isolated as a yellow oil and used without further purification. ¹H NMR (360MHz, d₆-DMSO) δ 0.97 – 1.08 (4H,m), 2.69 – 2.79 (1H,m), 3.76 (3H,s). 12.80 – 13.40 (1H,br s).

25

30 Sodium acetate trihydrate (17g, 0.13 mol) and 5,5-dimethyl-1,3-cyclohexandione (14g, 0.1 mol) in AcOH (117mL) was heated to 70°C. A

solution of the oxime (18g, 0.1 mol) in AcOH (58mL) was added via a dropping funnel, whilst simultaneously adding zinc dust (10g) over a period of 15 min, maintaining the temperature between 70 -80°C. The solution was heated at 100°C for 2h, after which time the mixture was cooled to room temperature, poured into ice-water (400mL) and extracted with DCM (3x100mL). The combined organic layers were washed with water (200mL), dried (MgSO₄) and evaporated. The resultant yellow oil solidified on standing at 0°C, whereupon isohexane/ether was added and the resultant pyrrole (6.5g, 25%) isolated as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ 0.89 – 0.93 (2H,m), 1.09 (6H,s), 1.21 – 1.26 (2H,m), 2.33 (2H,s) 2.53 – 2.65 (3H,m) 3.87 (3H,s), 8.90 – 9.06 (1H,br s). MS (ES⁺) 262 (M+1).

Step 2: 3-Cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylic acid

In the same way as described for Intermediate 1, Step 2, using methyl 3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate the acid (3.8g, 100%) was isolated as a colourless solid. ¹H NMR (250 MHz, d₆-DMSO) δ 0.70 – 0.79 (2H,m), 1.00 (6H,s), 1.18 – 1.28 (2H,m), 2.22 (2H,s), 2.63 (2H,s), 2.74 – 2.86 (1H,m), 11.74 – 11.82 (1H,br s). MS (ES⁺) 248 (M+1).

Step 3: 3-Cyclopropyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A solution of the acid (511mg, 2.1mmol) in DMSO (8mL) and water (2mL) was heated at 150°C for 18h. After this time the mixture was diluted with EtOAc (50mL) and washed with water (2x50mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The residue was triturated with ether/hexane to afford the title pyrrole (197mg, 47%) as a colourless solid. ¹H NMR (250MHz, CDCl₃) δ 0.45 –

0.52 (2H,m), 0.84 – 0.91 (2H,m), 1.10 (6H,s), 2.26 – 2.35 (3H,m), 2.61 (2H,s), 6.23 (1H,d, J = 3Hz), 7.94 – 8.22 (1H,br s). MS(ES⁺) 204 (M+1).

Step 4: 3-Cyclopropyl-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-

5 tetrahydroindol-4-one

In the same way as described for example 1 using 3-cyclopropyl-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one the title compound (38mg, 41%) was isolated as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ

10 0.53 – 0.57 (2H,m), 0.90 – 0.94 (2H,m), 1.10 (6H,s), 2.38 – 2.43 (3H,m),
~~2.91 (2H,s), 6.68 (1H,s), 7.22 – 7.27 (2H,m), 7.81 (1H,d of t, J = 8.1 and~~
2.0Hz), 8.50 – 8.55 (1H,m). MS (ES⁺) 281 (M+1).

Example 4

15

3-Ethyl-6,6-dimethyl-1-(pyrimidin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indole-4-one (100mg, 0.52mmol), K₂CO₃ (87mg, 0.63mmol), copper (I) bromide (15mg, 0.1mmol) and 2-chloropyrimidine (71mg, 0.63mmol) in DMF (1mL) were
20 heated at 180°C for 24h. More copper (I) bromide (15mg, 0.1mmol) and 2-chloropyrimidine (50mg) were added and heating continued for a further 24h. The DMF was evaporated and the residue partitioned between water and DCM. The organic layer was separated and the
25 aqueous phase extracted with DCM (2x). The combined organic layers were washed with water, dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel, eluting with 4:1 isohexane: EtOAc, to afford the title compound (35mg, 25%) as a yellow solid. mp 111-114°C. Found: C, 71.07; H, 6.98; N, 15.20%. Calc C₁₆H₁₉N₃O: C, 71.35;

30 H, 7.11; N, 15.60%. ¹H NMR (360MHz, d₆-DMSO) δ 1.06 (6H,s), 1.15 (3H,t, J = 7.4Hz), 2.30 (2H,s), 2.67 (2H,q, J = 7.3Hz), 3.23 (2H,s), 7.44

(1H,t, J = 4.8Hz), 7.47 (1H,s), 8.86 (2H,d, J = 4.8Hz). MS (ES⁺) 270 (M+1).

Example 5

5

6,6-Dimethyl-3-ethyl-1-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described for Example 4 using 2-bromothiazole, the title compound (45mg, 31%) was isolated as a cream solid. mp 58-60°C.

10 Found: C, 64.94; H, 6.25; N, 10.27%. Calc. C₁₅H₁₈N₂OS.0.1(H₂O): C, 65.23, H, 6.64; N, 10.14%. ¹H NMR (360MHz, d₆-DMSO) δ 1.06 (6H,s), 1.15 (3H,t, J = 7.4Hz), 2.31 (2H,s), 2.66 (2H,q, J = 7.4Hz), 3.01 (2H,s), 7.14 (1H,s) 7.64 (1H,d, J = 3.5Hz), 7.71 (1H,d, J = 3.5Hz). MS (ES⁺) 275 (M+1).

15

Example 6

6,6-Dimethyl-3-ethyl-1-(3-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one

20 6,6-Dimethyl-3-ethyl-4,5,6,7-tetrahydro-1H-indol-4-one (50mg, 0.26mmol), copper acetate (71mg, 0.39mmol), 3-fluorophenyl boronic acid (73mg, 0.52mmol) and triethylamine (73μL, 0.52mmol) and triethylamine (73μL, 0.52mmol) in DCM (1mL) was stirred at room temperature for 48h. The crude reaction mixture was poured onto a
25 bond elut tube (Anachem 1225-6034 10g/60mL) and eluted using isohexane : EtOAc (100:0 → 5:1) to afford a yellow solid. The solid was triturated in ether to afford the title compound (15mg, 20%) as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ 1.08 (6H,s), 1.22 (3H,t, J = 7.4Hz), 2.36 (2H,s), 2.62 (2H,s), 2.81 (2H,q, J = 7.4Hz), 6.57 (1H,s), 7.02
30 - 7.11 (3H,m), 7.41 - 7.45 (1H,m). MS (ES⁺) 286 (M+1).

Example 76,6-Dimethyl-3-ethyl-1-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydroindol-4-one

5

In the same way as described in Example 6 using 4-trifluoromethylbenzene boronic acid, the title compound (13mg, 10%) was isolated as a colourless solid. ^1H NMR (360MHz, CDCl_3) δ 1.08 (6M,s), 1.23 (3H,t, J = 7.4Hz), 2.38 (2H,s), 2.64 (2H,s), 2.82 (2H,q, J = 7.4Hz), 6.60 (1H,s), 7.41 (2H,d, J = 8.4Hz), 7.75 (2H,d, J = 8.4Hz). MS (ES⁺) 336 (M+1).

10

Example 815 6,6-Dimethyl-3-ethyl-1-(4-methylphenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-methylbenzene boronic acid, the title compound (65mg, 59%) was isolated as a colourless solid. Found: C, 80.53; H, 8.30; N, 4.76%. Calc. $\text{C}_{19}\text{H}_{23}\text{NO} \cdot 0.15(\text{H}_2\text{O})$: C, 80.33; H, 8.27; N, 4.93%. ^1H NMR (360MHz, CDCl_3) δ 1.06 (6H,s), 1.22 (2H,t, J = 7.4Hz), 2.27 (2H,s), 2.35 (3H,s), 2.58 (2H,s), 2.80 (2H,q, J = 7.4Hz), 6.53 (1H,s), 7.17 (2H,d, J = 8.3Hz), 7.26 (2H,d, J = 8.3Hz). MS (ES⁺) 282 (M+1).

20

25 Example 91-(4-Chlorophenyl)-6,6-dimethyl-3-ethyl-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 4-chlorobenzene boronic acid, the title compound (38mg, 32%) was isolated as a colourless solid. Found: C, 70.18; H, 6.58; N, 4.43%. Calc. $\text{C}_{18}\text{H}_{20}\text{ClNO} \cdot 0.4(\text{H}_2\text{O})$:

30

C, 69.96; H, 6.78; N, 4.53%. ¹H NMR (360MHz, CDCl₃) δ 1.07 (6H,s), 1.22 (3H,t, J = 7.4Hz), 2.30 (2H,s), 2.58 (2H,s), 2.80 (2H,q, J = 7.4Hz), 6.54 (1H,s), 7.24 (1H,d, J = 8.7Hz), 7.44 (1H,d, J = 8.7Hz). MS (ES⁺) 302/304 (M+1).

5

Example 10

6,6-Dimethyl-3-ethyl-1-(4-fluorophenyl)-4,5,6,7-tetrahydroindol-4-one

- 10 In the same way as described in Example 6 using 4-fluorobenzene boronic acid, the title compound (50mg, 45%) was isolated as a colourless solid. Found: C, 74.76; H, 6.98; N, 4.80%. Calc. C₁₈H₂₀FNO.0.2(H₂O): C, 74.82; H, 7.12; N, 4.85%. ¹H NMR (360MHz, d₆-DMSO) δ 0.99 (6H,s), 1.15 (3H,t, J = 7.5Hz), 2.25 (2H,s), 2.63 (2H,s), 2.66 (2H,q, J = 7.5Hz), 15 6.79 (1H,s), 7.37 (2H,dd, J = 8.7 and 8.7Hz), 7.49 (2H,dd, J = 8.7 and 4.9Hz). MS (ES⁺) 286 (M+1).

Example 11

- 20 6,6-Dimethyl-3-ethyl-1-(3-methylphenyl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 6 using 3-methylbenzene boronic acid, the title compound (50mg, 31%) was isolated as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ 1.07 (6H,s), 1.23 (3H,t, J = 7.5Hz), 25 2.31 (2H,s), 2.43 (3H,s), 2.59 (2H,s), 2.81 (2H,q, J = 7.5Hz), 6.55 (1H,s), 7.07 – 7.11 (2H,m), 7.19 (1H,d, J = 7.5Hz). 7.35 (1H,dd, J = 7.6 and 7.6Hz). MS (ES⁺) 282 (M+1).

Example 126,6-Dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one5 Step 1: 6,6-Dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A solution of 5,5-dimethyl-1,3-cyclohexandione (30g, 0.21mol), aminoacetaldehyde dimethyl acetal (35mL, 0.32mol) and p-toluenesulphonic acid hydrate (1.5g, 8mmol) in toluene (250mL) were
10 heated at reflux for 4h using Dean-Stark apparatus to remove the water.

The toluene was evaporated and the residue dissolved in 3N HCl (250mL). The solution was heated at 60°C for 6h. After this time the mixture was cooled to room temperature and extracted with DCM (6x). The combined organic layers were dried (MgSO₄), evaporated and the
15 residue chromatographed on silica gel, eluting with isohexane: EtOAc (4:1 → 1:1). The fractions containing the desired product were combined, evaporated and the residue triturated with ether. The title compound (1.8g, 5%) was isolated as a cream solid. mp 177 - 178°C. ¹H
NMR (360MHz, d₆ - DMSO) δ 1.02 (6H,s), 2.19 (2H,s), 2.63 (2H,s), 6.23
20 (1H,t, J = 3.9Hz), 6.71 (1H,t, J = 3.9Hz). MS (ES⁺) 164 (M+1).

Step 2: 6,6-Dimethyl-2-thiocyanato-4,5,6,7-tetrahydro-1H-indol-4-one

Potassium thiocyanate (1.2g, 12.3mmol) was dissolved in MeOH (4mL)
25 and cooled to -70°C. The mixture was treated with bromine (0.31mL, 6.1mmol), maintaining the temperature below -60°C. After addition the mixture was warmed to -30°C and a solution of the indolone (1g, 6.1mmol) in MeOH (25mL) was added dropwise. The mixture was stirred for 30 min at -30°C then allowed to warm to room temperature
30 and stirred for 3h. The mixture was poured onto ice water (30mL), the MeOH evaporated and the aqueous phase extracted with DCM (2x). The

combined organic layers were washed with water, NaHCO_3 (sat.) then separated and dried (Na_2SO_4). The solvent was evaporated and the residue triturated with ether. The title compound (0.83g, 62%) was isolated as a beige solid. ^1H NMR (360MHz, d_6 – DMSO) δ 1.03 (6H,s) 2.25 (2H,s), 2.68 (2H,s), 6.83 (1H,d, $J = 1.9\text{Hz}$), 12.44 (1H,br s). MS (ES⁺) 221 (M+1).

Step 3: 6,6-Dimethyl-2-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one

To a stirred solution of 6,6-dimethyl-2-thiocyanato-4,5,6,7-tetrahydro-1H-indol-4-one (400mg, 1.8mmol) and MeI (124 μL , 2.0mmol) in MeOH (10mL) at -5°C was added a solution of KOH (117mg, 2.1mmol) in 1:1 MeOH/water (6mL), maintaining the temperature below 0°C . The mixture was stirred for 3h at room temperature, after which time the MeOH was removed and the residue partitioned between DCM and water. The organic layer was separated and the aqueous phase re-extracted with DCM. The combined organic layers were dried (Na_2SO_4) and evaporated to afford the title compound (350mg, 88%) as a colourless solid. mp $195 - 196^\circ\text{C}$. Found: C, 62.20; H, 7.13; N, 6.34%. Calc. $\text{C}_{11}\text{H}_{15}\text{NOS} \cdot 0.2(\text{H}_2\text{O})$: C, 62.06; H, 7.29; N, 6.58%. ^1H NMR (360MHz, d_6 – DMSO) δ 1.02 (6H,s), 2.19 (2H,s), 2.34 (3H,s), 2.61 (2H,s), 6.30 (1H,d, $J = 2.4\text{Hz}$), 11.59 (1H,br s). MS (ES⁺) 210 (M+1).

Step 4: 6,6-Dimethyl-3-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one

6,6-Dimethyl-2-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one (350mg, 1.7mmol) was heated at reflux in trifluoroacetic acid (4mL) and 1,2-dichloroethane (4mL) for 5h. After this time the mixture was evaporated and the residue partitioned between water (10mL) and DCM (10mL). The organic layer was separated and the aqueous phase extracted with DCM (2x). The combined organic layers were dried

(Na₂SO₄) and evaporated. The residue was chromatographed on silica gel, eluting with hexane: EtOAc (4:1), to afford the title compound (60mg, 17%) as a pink solid. ¹H NMR (360MHz, d₆ – DMSO) δ 1.01 (6H,s), 2.18 (2H,s), 2.27 (3H,s), 2.61 (2H,s), 6.53 (1H,d, J = 2.2Hz), 11.31 (1H,br s). MS (ES⁺) 210 (M+1).

Step 5: 6,6-Dimethyl-3-methylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

10 In the same way as described in Example 1 using 6,6-dimethyl-3-methylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (20mg, 30%) was isolated as a colourless solid. ¹H NMR (360MHz, d₆ – DMSO) δ 0.97 (6H,s) 2.24 (2H,s) 2.30 (3H,s), 2.92 (2H,s), 7.03 (1H,s), 7.37 (1H,dd, J = 7.1 and 5.0Hz), 7.60 (1H,d, J = 8.1Hz), 7.95 (1H,d of t, J = 7.7 and 1.9Hz), 8.50 – 8.53 (1H,m). MS (ES⁺) 287 (M+1).

Example 13

6,6-Dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

20

Step 1: 6,6-Dimethyl-2-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one

In the same way as described for Example 12, Step 3 using ethyl iodide, the title compound (385mg, 48%) was isolated as a colourless solid.

25 ¹H NMR (360MHz, d₆ – DMSO) δ 1.02 (6H,s), 1.13 (3H,t, J = 7.2Hz), 2.20 (2H,s), 2.62 (2H,s), 2.68 (2H,q, J = 7.2Hz), 6.36 (1H,d, J = 2.3Hz), 11.56 (1H,br s). MS (ES⁺) 224 (M+1).

Step 2: 6,6-Dimethyl-3-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one

In the same way as described in Example 12, Step 4 using 6,6-dimethyl-2-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound
5 (100mg, 26%) was isolated as a colourless solid. ¹H NMR (360MHz, d₆ - DMSO) δ 1.01 (6H,s), 1.14 (3H,t, J = 7.4Hz), 2.19 (2H,s), 2.62 (2H,s), 2.75 (2H,q, J = 7.2Hz), 6.64 (1H,d, J = 2.3Hz), 11.33 (1H,br s). MS (ES⁺) 224 (M+1).

10 Step 3: 6,6-Dimethyl-3-ethylthio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 6,6-dimethyl-3-ethylthio-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (80mg,
15 60%) was isolated as a cream solid. mp 158 - 159°C. Found: C, 67.49; H, 6.60; N, 9.08%. Calc. C₁₇H₂₀N₂OS.0.1(H₂O): C, 67.56; H, 6.74; N, 9.27%. ¹H NMR (360MHz, d₆ - DMSO) δ 1.02 (6H,s), 1.25 (3H,t, J = 7.3Hz), 2.30 (2H,s), 2.86 (2H,q, J = 7.3Hz), 2.97 (2H,s), 7.18 (1H,s), 7.43 (1H,dd, J = 7.5 and 4.9Hz), 7.65 (1H,d, J = 8.1Hz), 8.02 (1H,d of t, J = 7.9
20 and 1.9Hz), 8.57 - 8.62 (1H,m). MS (ES⁺) 301 (M+1).

Example 14

25 6,6-Dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

Step 1: 6,6-Dimethyl-2-(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one

30 In the same way as described for Example 12, Step 3 using benzyl bromide, the title compound (457mg, 72%) was obtained as a cream

solid. mp 148-150°C. Found: C, 70.90; H, 6.46; N, 5.02%. Calc.

C₁₇H₁₉NOS.0.15(H₂O): C, 70.87; H, 6.75; N, 4.86%. ¹H NMR (360MHz, CDCl₃) δ 1.07 (6H,s), 2.31 (2H,s), 2.47 (2H,s), 3.82 (2H,s), 6.67 (1H,d, J = 2.4Hz), 7.08 – 7.12 (2H,m), 7.23 – 7.26 (3H,m), 7.56 (1H,br s). MS (ES⁺)
5 286 (M+1).

Step 2: 6,6-Dimethyl-3-(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one

- 10 In the same way as described in Example 12, Step 4 using 6,6-dimethyl-
2(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one, the title
compound (64mg, 15%) was isolated as a cream solid. mp 220 - 223°C.
Found: C, 68.43; H, 6.31; N, 4.66%. Calc. C₁₇H₁₉NOS.0.65(H₂O): C,
68.72; H, 6.89; N, 4.71%. ¹H NMR (360MHz, CDCl₃ + d₄-MeOH) δ 1.00
15 (6H,s), 2.24 (2H,s), 2.53 (2H,s), 3.92 (2H,s), 6.34 (1H,s), 7.04 – 7.11
(5H,m). MS (ES⁺) 286 (M+1).

Step 3: 6,6-Dimethyl-3(phenylmethyl)thio-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

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- In the same way as described in Example 1 using 6,6-dimethyl-3-
(phenylmethyl)thio-4,5,6,7-tetrahydro-1H-indol-4-one, the title
compound (17mg, 27%) was obtained as a cream solid. mp 190 - 192°C.
Found: C, 70.66; H, 5.84; N, 7.50%. Calc. C₂₂H₂₂N₂OS.0.1(CH₂Cl₂).0.2
25 (H₂O): C, 70.86; H, 6.08; N, 7.48%. ¹H NMR (360MHz, CDCl₃) δ 1.11
(6H,s), 2.43 (2H,s), 2.94 (2H,s), 4.14 (2H,s), 6.89 (1H,s), 7.19 – 7.34
(7H,m), 7.79 – 7.84 (1H,m), 8.52 – 8.56 (1H,m). MS (ES⁺) 363 (M+1).

Example 156,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

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Step 1: 6,6-Dimethyl-1-(triisopropylsilyl)-4,5,6,7-tetrahydroindol-4-one

A solution of 6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one (3.8g, 23mmol) in DMF (25mL) was cooled to 0°C and NaH (1.02g of a 60% dispersion in mineral oil, 26mmol) was added portionwise. The mixture was stirred for 30 min then triisopropylsilyl chloride (5.6mL, 26mmol) was added at 0°C and stirring continued for 1 hr. The mixture was warmed to room temperature then extracted with ether (3x). The combined organic layers were dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel, eluting with isohexane: EtOAc (9:1), to give the title compound (2.9g, 39%) as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ 1.11 (6H,s), 1.14 (18H,d, J = 7.5Hz) 1.51 (3H,heptet, J = 7.5Hz), 2.34 (2H,s), 2.71 (2H,s), 6.64 (1H,d, J = 3.1Hz), 6.71 (1H,d, J = 3.1Hz). MS (ES⁺) 320 (M+1).

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Step 2: 3-Bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one

A solution of 6,6-dimethyl-1-(triisopropylsilyl)-4,5,6,7-tetrahydroindol-4-one (410mg, 1.28mmol) in THF (20mL) was cooled to -70°C and N-bromosuccinimide (228mg, 1.28mmol) was added. Stirring was continued at -70°C for 1h then warmed to room temperature. After attaining room temperature, tetrabutylammonium fluoride (1.28mL of a 1.0M solution in THF, 1.28mmol) was added and stirring continued for 5 min. Ether (20mL) was added, followed by water, and the organic layer separated. The aqueous phase was extracted with ether and the combined organic layers were dried (MgSO₄) and evaporated. The

30

residue was purified on silica gel, eluting with DCM, to give the title compound (210mg, 68%) as a colourless solid. ^1H NMR (360MHz, d_6 - DMSO) δ 1.02 (6H,s), 2.22 (2H,s), 2.64 (2H,s), 6.89 (1H,d, J = 2.4Hz), 11.58 (1H,br s). MS (ES^+) 242/244 ($\text{M}+1$).

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Step 3: 3-Bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one, the title compound (600mg, 61%) was isolated as a pale yellow solid. mp 168 - 170°C. Found: C, 56.00; H, 4.64; N, 8.75%. Calc. $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}$. 0.1 (H_2O): C, 56.13; H, 4.77; N, 8.73%. ^1H NMR (360MHz, d_6 - DMSO) δ 1.03 (6H,s), 2.33 (2H,s), 2.98 (2H,s), 7.47 (1H,dd, J = 7.5 and 5.5Hz). 7.55 (1H,s). 7.66 (1H,d, J = 8.3Hz), 8.04 (1H,d or t, J = 7.7 and 1.9Hz), 8.57 - 8.62 (1H,m), MS (ES^+) 319/321 ($\text{M}+1$).

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Step 4: 6,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

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A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (100mg, 0.31mmol) and 2-(n-tributylstannyl)thiazole (175mg, 0.47mmol) in dioxan (10mL) was degassed with nitrogen for 30 min. Tetrakis (triphenylphosphine) palladium (75mg, 0.06mmol) was added and the mixture heated at reflux for 24h. The solvent was evaporated and the residue purified on silica gel, eluting with isohexane: EtOAc (9:1 \rightarrow 1:1). The fractions containing the desired product were combined and evaporated. The resultant orange solid was triturated with isohexane and the title compound (75mg, 74%) isolated as a cream solid. mp 166 - 168°C. Found: C, 66.26; H, 5.27; N, 12.66%. Calc. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$. 0.2(H_2O): C, 66.11; H, 5.36; N, 12.85%. ^1H NMR

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(360MHz, CDCl₃) δ 1.15 (6H,s), 2.50 (2H,s), 3.04 (2H,s), 7.31 – 7.35 (2H,m), 7.45 (1H,d, J = 6.3Hz), 7.78 (1H,d, J = 3.2Hz), 7.86 (1H,d of t, J = 7.8 and 1.9Hz), 7.91 (1H,s), 8.56 – 8.60 (1H,m). MS (ES⁺) 324 (M+1).

5 Example 16

6,6-Dimethyl-3-phenyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-
10 tetrahydroindol-4-one (100mg, 0.31mmol), phenylboronic acid (153mg, 1.25mmol), tetrakis(triphenylphosphine)palladium (50mg, 0.04mmol) and Na₂CO₃ (197mg, 1.9mmol) in ethylene glycol dimethyl ether (10mL) and water (4mL) was heated at reflux for 8h. The solvent was
evaporated and the residue partitioned between DCM and aqueous
15 K₂CO₃ (10% (w/v)). The organic layer was separated and the aqueous phase re-extracted with DCM (2x). The combined organic layers were washed with water, dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel, eluting with isohexane: EtOAc (9:1), to afford the title compound (60mg, 61%) as a yellow solid. mp 160-162°C.
20 Found: C, 78.23; H, 6.26; N, 8.57%. Calc. C₂₁H₂₀N₂O.0.35(H₂O): C, 78.16; H, 6.47; N, 8.68%. ¹H NMR (360MHz, CDCl₃) δ 1.13 (6H,s), 2.45 (2H,s), 2.99 (2H,s), 7.17 (1H,s), 7.24 – 7.38 (5H,m), 7.67 (2H,d, J = 7.2Hz), 7.86 (1H,d of t, J = 7.9 and 1.9Hz), 8.56 – 8.61 (1H,m). MS (ES⁺) 317 (M+1).

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Example 176,6-Dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

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In the same way as described in Example 15, Step 4 using 2-(tributylstannyl)pyridine, the title compound (40mg, 40%) was isolated as a cream solid. mp 171-174°C. Found: C, 74.55; H, 5.89; N, 12.61%.

Calc. C₂₀H₁₉N₃O.0.35(H₂O): C, 74.21; H, 6.13; N, 12.98%. ¹HNMR

10 (360MHz, CDCl₃) δ 1.14 (6H,s), 2.49 (2H,s), 3.03 (2H,s), 7.15 (1H,dd, J = 6.3 and 3.8Hz), 7.31 (1H,dd, J = 7.5 and 4.9Hz), 7.48 (1H,d, J = 8.2Hz), 7.70 – 7.73 (2H,m), 7.86 (1H,d of t, J = 7.8 and 1.9Hz), 8.32 (1H,d, J = 8.1Hz), 8.55 – 8.59 (2H,m). MS (ES⁺). 318 (M+1).

15 Example 186,6-Dimethyl-1-(pyridin-2-yl)-3-vinyl-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using

20 tributyl(vinyl)tin, the title compound (45mg, 54%) was isolated as a cream solid. mp 150 - 154°C. ¹H NMR (360MHz, CDCl₃) δ 1.11 (6H,s), 2.40 (2H,s), 2.93 (2H,s), 5.18 (1H,dd, J = 11 and 1.8Hz), 5.72 (1H,dd, J = 18 and 1.8Hz), 7.22 (1H,dd, J = 18 and 11Hz), 7.26 – 7.35 (3H,m), 7.85 (1H,d of t, J = 7.7 and 1.9Hz), 8.55 – 8.58 (1H,m). MS (ES⁺) 267 (M+1).

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Example 196,6-Dimethyl-3-phenylmethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

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A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (100mg, 0.31mmol), benzyltributylstannane (253mg, 0.68mmol) and dichlorobis(triphenylphosphine)palladium (50mg, 0.08mmol) in hexamethylphosphoramide (1mL) was heated at 10 70°C for 48h. The mixture was cooled to room temperature, diluted with DCM (2mL), and the solution chromatographed on silica gel, eluting with isohexane: EtOAc (4:1). The title compound (45mg, 43%) was isolated as a colourless solid. mp 111 - 113°C. Found: C, 79.7; H, 6.7; N, 8.3%. Calc. C₂₂H₂₂N₂O: C, 79.97; H, 6.71; N, 8.48%. ¹H NMR 15 (360MHz, CDCl₃) δ 1.11 (6H,s), 2.39 (2H,s), 2.93 (2H,s), 4.17 (2H,s), 6.61 (1H,s), 7.16 - 7.34 (7H,m), 7.77 (1H, d of t, J = 7.7 and 1.9Hz), 8.50 - 8.53 (1H,m). MS (ES⁺) 331 (M+1).

Example 20

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6,6-Dimethyl-3-(oxazol-2-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 2-tributylstannyloxazole, the title compound (50mg, 52%) was afforded as 25 a cream solid. mp 194 - 196°C. Found: C, 70.30; H, 5.25; N, 13.48%. Calc. C₁₈H₁₇N₃O₂: C, 70.34; H, 5.58; N, 13.67%. ¹H NMR (400MHz, CDCl₃) δ 1.13 (6H,s), 2.50 (2H,s), 3.00 (2H,s), 7.20 (1H,s), 7.36 (1H,dd, J = 6.7 and 4.3Hz), 7.41 (1H,d, J = 7.4Hz), 7.73 (1H,s), 7.75 (1H,s), 7.89 30 (1H,d of t, J = 6.9 and 1.7Hz), 8.57 - 8.60 (1H,m). MS (ES⁺) 308 (M+1).

Example 216,6-Dimethyl-1-(pyridin-2-yl)-3-(thiazol-5-yl)-4,5,6,7-tetrahydroindol-4-one

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In the same way as described in Example 15, Step 4 using 5-tributylstannylthiazole, the title compound (73mg, 72%) was obtained as a yellow solid. mp 167 - 169°C. Found: C, 64.96; H, 5.23; N, 12.01%.

Calc. C₁₈H₁₇N₃OS.0.1(Et₂O).0.45 (H₂O): C, 65.20; H, 5.62; N, 12.40%. ¹H

10 NMR (400MHz, CDCl₃) δ 1.14 (6H,s), 2.47 (2H,s), 2.97 (2H,s), 7.33 - 7.39 (3H,m), 7.90 (1H,d of t, J = 7.7 and 1.9Hz), 8.41 (1H,s), 8.57 - 8.60 (1H,m), 8.70 (1H,s). MS (ES⁺) 324 (M+1).

Example 22

15

6,6-Dimethyl-3-phenylamino-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A suspension of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (50mg, 0.16mmol), aniline (17μL, 0.19mmol), sodium *tert*-butoxide (18mg, 0.19mmol) tris(dibenzylideneacetone)dipalladium (7.2mg, 0.008mmol) and (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (9.8mg, 0.016mmol) in toluene (3mL) was heated at reflux for 3h. The toluene was evaporated and the residue chromatographed on silica gel, eluting with isohexane: EtOAc (9:1 → 4:1). The title compound (23mg, 43%) was isolated as a yellow solid. mp 135 - 138°C. Found: C, 73.98; H, 6.10; N, 12.33%. C₂₁H₂₁N₃O.0.45(H₂O): C, 74.29; H, 6.50; N, 12.38%. ¹H NMR (360MHz, d₆-DMSO) δ 1.07 (6H,s), 2.37 (2H,s), 3.03 (2H,s), 6.81 (1H,t, J = 7.4Hz), 7.08 (2H,d, J = 7.7Hz), 7.25 - 7.29 (2H,m), 7.41 (1H,dd, J = 7.2 and

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25

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and 4.9Hz), 7.72 (1H,d, J = 8.1Hz), 8.01 (1H,d of t, J = 7.6 and 1.8Hz), 8.16 (1H,s), 8.57 – 8.60 (1H,m). MS (ES⁺) 332 (M+1).

Example 23

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6,6-Dimethyl-1-(pyridin-2-yl)-3-(pyridin-2-ylamino)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 22 using 2-aminopyridine, the
10 title compound (20mg, 23%) was isolated as a yellow solid. mp 180 -
183°C. ¹H NMR (360MHz, CDCl₃) δ 1.13 (6H,s), 2.41 (2H,s), 3.04 (2H,s),
6.65 – 6.69 (1H,m), 6.73 (1H,d, J = 8.5Hz), 7.24 (1H,dd, J = 7.4 and
4.9Hz), 7.44 – 7.48 (2H,m), 7.83 (1H,d of t, J = 7.9 and 1.9Hz) 7.91
(1H,s), 8.26 – 8.30 (1H,m), 8.53 – 8.57 (1H,m), 8.74 (1H,s). MS (ES⁺) 333
15 (M+1).

Example 24

6,6-Dimethyl-3-ethyl-1-(6-methylpyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

20 one

In the same way as described in Example 1 using 2-fluoro-6-
methylpyridine, the title compound (15mg, 17%) was isolated as a cream
solid. ¹H NMR (360MHz, CDCl₃) δ 1.09 (6H,s), 1.23 (3H,t, J = 7.4Hz)
25 2.37 (2H,s), 2.58 (3H,s), 2.81 (2H,q, J = 7.4Hz), 2.89 (2H,s), 6.89 (1H,s),
7.07 – 7.12 (2H,m), 7.69 (1H,t, J = 7.8Hz). MS (ES⁺) 283 (M+1).

Example 256,6-Dimethyl-3-(4-methylthiazol-5-yl)-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

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In the same way as described in Example 15, Step 4 using 2-(tributylstannyl)-4-methylthiazole the title compound (52mg, 19mg) was isolated. ¹H NMR (400MHz, d₆-DMSO) δ 1.06 (6H,s), 2.37 (3H,s), 2.43 (2H,s), 3.01 (2H,s) 7.16 (1H,s), 7.50 (1H,dd, J = 7.3 and 4.9Hz), 7.77 (1H,d, J = 8.2Hz), 7.94 (1H,s), 8.06 (1H,d of t, J = 8.0 and 1.7Hz), 8.61 – 8.63 (1H,m). MS (ES⁺) 338 (M+1).

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Example 26

15 3-(4-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one (50mg, 0.16mmol) and

20 tetrakis(triphenylphosphine)palladium (15mg, 0.01mmol) in ethylene glycol dimethyl ether (2mL) at 45°C was degassed with nitrogen for 30 min. A degassed solution of Cs₂CO₃ (104mg, 0.16mmol) in water (1mL) was added followed by 4-chlorophenylboronic acid (25mg, 0.16mmol). The solution was heated at 100°C for 18h then filtered through celite.

25 The filtrate was partitioned between DCM and water. The organic phase was separated, dried (MgSO₄) and evaporated. The residue was purified by column chromatography, eluting with isohexane: EtOAc (3:1) to give the title compound (6mg, 11%) as a colourless solid.

¹H NMR (360MHz, d₆-DMSO) δ 1.05 (6H,s), 2.37 (2H,s), 3.01 (2H,s), 7.38 (2H,d, J = 8.5Hz), 7.46 – 7.50 (1H,m), 7.56 (1H,s), 7.68 – 7.74 (3H,m), 8.05 – 8.09 (1H,m), 8.59 – 8.63 (1H,m). MS (ES⁺) 351/353 (M+1).

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Example 273-(3-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-5 4-one

In the same way as described in Example 26 using

3-chlorophenylboronic acid, the title compound (71mg, 43%) was isolated as a colourless solid. ¹H NMR (360MHz, CDCl₃) δ 1.13 (6H,s), 2.46

10 (2H,s), 2.98 (2H,s), 7.20 (1H,s), 7.23 – 7.39 (4H,m), 7.60 (1H,t of d, J = 7.3 and 1.5Hz), 7.66 (1H,t, J = 1.8Hz), 7.88 (1H,d of t, J = 7.9 and 1.9Hz), 8.57 – 8.60 (1H,m). MS (ES⁺) 351/353 (M+1).

Example 28

15

3-(2-Chlorophenyl)-6,6-dimethyl-1-(pyridin-2-yl)-4,5,6,7-tetrahydroindol-
4-one

In the same way as described in Example 26 using

20 2-chlorophenylboronic acid, the title compound (44mg, 27%) was isolated as a colourless solid. ¹H NMR (400MHz, CDCl₃) δ 1.14 (6H,s), 2.40 (2H,s), 3.02 (2H,s), 7.16 (1H,s), 7.23 – 7.26 (2H,m), 7.30 (1H,dd, J = 7.4 and 5.0Hz), 7.38 (1H,d, J = 8.1Hz), 7.41 – 7.44 (2H,m), 7.87 (1H,d of t, J = 7.6 and 1.9Hz), 8.56 – 8.58 (1H,m). MS (ES⁺) 351/353 (M+1).

25

Example 296,6-Dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

5

Step1: 3-Bromo-6,6-dimethyl-1-(pyridin-3-yl)-4,5,6,7-tetrahydroindol-4-one

10 In the same way as described in Example 4 using 3-bromopyridine, the title compound (72mg, 8%) was isolated as a brown solid. ¹H NMR (360MHz, d₆-DMSO) δ 1.00 (6H,s) 2.31 (2H,s), 2.71 (2H,s), 7.40 (1H,s), 7.60 (1H,dd, J = 8.4 and 4.8Hz), 7.95 – 7.99 (1H,m), 8.67 – 8.70 (1H,m), 8.73 – 8.76 (1H,m). MS (ES⁺) 319/321 (M+1)

15 Step 2: 6,6-Dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

20 In the same way as described in Example 15, Step 4 using 6,6-dimethyl-1-(pyridin-3-yl)-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (12mg, 10%) was isolated as a colourless solid. ¹H NMR (400MHz, d₆-DMSO) δ 1.05 (6H,s), 2.42 (2H,s), 2.75 (2H,s) 7.61 – 7.65 (2H,m), 7.78 – 7.81 (2H,m), 8.05 – 8.08 (1H,m), 8.70 – 8.71 (1H,m). MS (ES⁺) 324 (M+1).

Example 301-(5-Chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

5

Step 1: 3-Bromo-1-(5-chloropyridin-2-yl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one

10 In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-1,2,3,4-tetrahydro-1H-indol-4-one and 2,5-dichloropyridine, the title compound (212mg, 36%) was isolated as a yellow solid.

Step 2: 1-(5-Chloropyridin-2-yl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

15

In the same way as described in Example 15, Step 4 using 3-bromo-1-(5-chloropyridin-2-yl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (73mg, 37%) was isolated as a pale yellow solid. ¹H NMR (400MHz, d₆-DMSO) δ 1.06 (6H,s), 2.44 (2H,s), 3.01 (2H,s), 7.63 (1H,d, J = 3Hz), 7.80 – 7.84 (2H,m), 8.00 (1H,s), 8.20 (1H,dd, J = 8.6 and 2.6Hz), 8.69 (1H,d, J = 2.6Hz). MS (ES⁺) 358/360 (M+1).

20 ¹H NMR (400MHz, d₆-DMSO) δ 1.02 (6H,s), 2.33 (2H,s), 2.97 (2H,s), 7.56 (1H,s), 7.71 (1H,d, J = 8.6Hz), 8.18 (1H,dd, J = 8.7Hz and 2.6Hz), 8.64 (1H,d, J = 2.6Hz). MS (ES⁺) 353/355 (M+1).

25

Example 316,6-Dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

5

Step 1: 3-Bromo-1-(6-chloropyridin-2-yl)-6,6-dimethyl-1,2,3,4-tetrahydroindol-4-one

10 In the same way as described in Example 1 using 3-bromo-6,6-dimethyl-1,2,3,4-tetrahydro-1H-indol-4-one and 2,6-dichloropyridine, the title compound (232mg, 40%) was isolated as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ 1.14 (6H,s), 2.42 (2H,s), 2.96 (2H,s), 7.17 (1H,s), 7.22 (1H,d, J = 8.0Hz), 7.33 (1H,d, J = 7.9Hz), 7.82 (1H,t, J = 7.8Hz). MS (ES⁺) 353/355 (M+1).

15

Step 2: 6,6-Dimethyl-3-(thiazol-2-yl)-1-(6-(thiazol-2-yl)pyridin-2-yl)-4,5,6,7-tetrahydroindol-4-one

20 In the same way as described in Example 15, Step 4 using 3-bromo-1-(6-chloropyridin-2-yl)-6,6-dimethyl-1,2,3,4-tetrahydroindol-4-one and 2-tributylstannylthiazole, the title compound (35mg; 13%) was isolated as a yellow solid. ¹H NMR (400MHz, CDCl₃) δ 1.21 (6H,s), 2.55 (2H,s), 3.24 (2H,s), 7.35 (1H,d, J = 3.1Hz), 7.50 – 7.53 (2H,m), 7.81 (1H,d, J = 3.1Hz), 7.97 – 8.02 (3H,m), 8.20 (1H,d, J = 7.8Hz). MS (ES⁺) 407 (M+1).

25

Example 321-(2-Cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

5

Step 1: 3-Bromo-1-(2-cyanophenyl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one

A solution of 3-bromo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indol-4-one
10 (670mg, 2.77mmol), 2-fluorobenzonitrile (0.3mL, 2.77mmol) and K₂CO₃
(957mg, 6.9mmol) in DMSO (10mL) was stirred at 100°C for 3h. The
mixture was cooled to room temperature, poured into water and
extracted into EtOAc (3x). The combined organic layers were washed
with water (2x), dried (MgSO₄) and evaporated. The title compound
15 (858mg, 91%) was isolated as a beige solid and used without further
purification. ¹H NMR (400MHz, CDCl₃) δ 1.10 (6H,s), 2.42 (2H,s), 2.51
(2H,s), 6.83 (1H,s), 7.42 (1H,dd, J = 7.9 and 0.9Hz), 7.64 (1H,dd, J = 7.7
and 1.1Hz), 7.78 (1H,dd, J = 7.9 and 1.5Hz), 7.85 (1H,dd, J = 7.7 and
1.4Hz). MS (ES⁺) 343/345 (M+1).

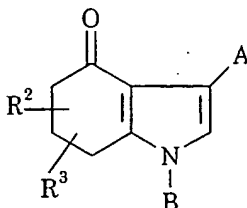
20

Step 2: 1-(2-Cyanophenyl)-6,6-dimethyl-3-(thiazol-2-yl)-4,5,6,7-tetrahydroindol-4-one

In the same way as described in Example 15, Step 4 using 3-bromo-1-(2-
25 cyanophenyl)-6,6-dimethyl-4,5,6,7-tetrahydroindol-4-one and 2-
tributylstannylthiazole, the title compound (200mg, 44%) was isolated
as a colourless solid. ¹H NMR (400MHz, d₆-DMSO) δ 1.05 (6H,s), 2.43
(2H,s), 2.53 (2H,s), 7.63 (1H,d, J = 3.3Hz), 7.75 – 7.80 (4H,m), 7.92
(1H,dd, J = 7.8 and 1.4Hz), 8.13 (1H,dd, J = 7.7 and 1.3Hz). MS (ES⁺)
30 348 (M+1).

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

5

where A is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, arylC₁₋₆alkyl, or aryl wherein the aryl group is optionally substituted by halogen, C₁₋₆ alkyl, CF₃, CN, NO₂ or NH₂, NR¹R¹⁰, S(O)_pR¹, heteroarylC₁₋₆alkyl or heteroaryl
 10 where heteroaryl is a 5- or 6-membered heteroaromatic ring as defined for B below;

B is phenyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one heteroatom is other than N, a 6-membered heteroaromatic
 15 ring containing 1, 2, 3 or 4 nitrogen atoms, each of which rings is optionally substituted by one or more substituents independently chosen from: cyano; C₁₋₆alkyl; C₁₋₆haloalkyl; halogen; S(O)_rR⁴; COR⁵; and aryl, arylC₁₋₆alkyl or a 5-membered ring having one or two unsaturations containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one
 20 heteroatom is other than N wherein the aryl ring or 5-membered ring is optionally substituted by one, two or three substituents independently chosen from halogen, CF₃, OCH₃, nitro and cyano; and when a nitrogen ring atom is present it is optionally substituted by oxygen;

R¹ is hydrogen; C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl or C₃₋₆cycloalkenyl each of which is optionally substituted by amino,
 25

C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkoxy, C₁₋₆alkylaminocarbonyl, one, two or three hydroxy groups, one, two or three halogen atoms or a four, five or six-membered saturated heterocyclic ring containing a nitrogen atom and optionally either an oxygen atom or a further nitrogen atom which ring is
 5 optionally substituted by C₁₋₄alkyl on the further nitrogen atom; aryl, arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl optionally substituted on the aryl ring by halogen, nitro, cyano, C₁₋₆alkylcarbonylamino, hydroxy or C₁₋₆alkoxy; or a five-membered aromatic ring containing 1, 2, 3 or 4 heteroatoms chosen from O, N and S provided that not more than one
 10 heteroatom is other than N, or a six-membered aromatic ring containing 1, 2, 3 or 4 nitrogen atoms, which ring is optionally substituted by halogen, C₁₋₆alkoxy, C₁₋₆alkylthio, aryl, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

R² and R³ are independently hydrogen or C₁₋₆alkyl or together with the carbon atom to which they are attached form a C₃₋₈ cycloalkyl group;

15 R⁴ is hydrogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, aryl or CH₂(CO)_mNR⁸R⁹;

R⁵ is NR⁶R⁷, C₁₋₆alkyl or C₁₋₆alkoxy;

R⁶ is independently as defined for R⁴;

R⁷ is aryl optionally substituted by halogen, nitro or cyano;

20 R⁸ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl, C₂₋₆alkenyl, C₂₋₆alkynyl; arylC₁₋₆alkyl, arylC₂₋₆alkenyl or arylC₂₋₆alkynyl optionally substituted on the aryl ring by halogen, nitro or cyano; thiophene or pyridine;

R⁹ is C₁₋₆alkyl; C₂₋₆alkenyl; C₂₋₆alkynyl; or phenyl optionally substituted by one, two or three substituents independently chosen from

25 halogen, CF₃, OCH₃, nitro and cyano;

R¹⁰ is hydrogen or C₁₋₆ alkyl;

R¹⁴ is hydrogen or C₁₋₆alkyl;

m is zero or 1;

p is zero, 1 or 2;

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q is 1 or 2;
r is 0, 1 or 2;
s is 0, 1 or 2; and
t is 0, 1 or 2.

5

2. A compound according to claim 1 wherein B is an optionally substituted phenyl or optionally substituted 6-membered heteroaromatic ring. The optional substituents are preferably one or two groups independently chosen from halogen, C₁₋₆alkyl, trifluoromethyl, cyano and an
10 ~~unsubstituted 5-membered heteroaromatic ring containing 1, 2, 3 or 4~~
heteroatoms chosen from O, N and S in which not more than one heteroatom is other than N.

3. A compound according to claim 1 or 2 wherein A is C₁₋₆alkyl,
15 C₂₋₆alkenyl, arylC₁₋₆alkyl or aryl wherein the aryl group is optionally substituted by a halogen atom or a C₁₋₆alkyl group, a 5- or 6-membered heteroaromatic ring optionally substituted by a halogen atom or C₁₋₆alkyl, NHR¹ or SR¹.

20 4. A compound according to claim 1, 2 or 3 wherein R¹ is C₁₋₆alkyl, C₁₋₄alkenyl, or C₃₋₆cycloalkyl each of which is optionally substituted by di(C₁₋₄alkyl)amino, C₁₋₄alkoxy, C₁₋₄alkylaminocarbonyl, one or two hydroxy groups or three fluorine atoms; phenyl or phenylC₁₋₄alkyl optionally
substituted on the phenyl ring by chlorine, fluorine, C₁₋₄alkoxy or
25 C₁₋₄alkylcarbonylamino; or a pyridine, thiophene, furan, pyrimidine, thiazole, imidazole, triazole or thiadiazole, each of which is unsubstituted or substituted by C₁₋₄alkyl, phenyl, fluorine or C₁₋₄alkylthio.

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5. A compound according to anyone of claims 1 to 4 wherein R^2 and R^3 are independently chosen from hydrogen and methyl.
6. A pharmaceutical composition comprising a compound according to any
5 one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
7. A compound according to anyone of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or
10 animal body by surgery, therapy or diagnosis.
8. Use of a compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment or prevention of a condition requiring the
15 administration of a ligand selective for GABA_A receptors containing the $\alpha 5$ subunit.
9. A method of treatment or prevention of a condition associated with GABA_A receptors containing the $\alpha 5$ subunit in a subject suffering from or
20 prone to such a condition which comprises administering to that subject a therapeutically or prophylactically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01799

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/04 A61K31/40 C07D403/04 C07D417/04 C07D209/08
 C07D417/14 C07D401/14 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 150 397 A (PARKE, DAVIS & COMPANY) 30 April 1969 (1969-04-30) page 9, line 17 - line 19 ---	1-3,5
X	BRIAN G. MCDONALD ET AL.: "Conversion of 2-Chloroallylamines into Heterocyclic Compounds. Part I. 2-Methylindoles, 1,5,6,7-Tetrahydro-3-methylindol-4-ones, and Related Heterocycles" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 15, - 1975 pages 1446-1450, XP002114574 LETCWORTH GB * page 1449, right column: compounds of formula XVII with X = 3-Me and R = Ph or p-ClC6H4 * --- -/--	1-3,5

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

7 September 1999

Date of mailing of the international search report

22/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 18792 A (MERCK SHARP & DOHME LTD.) 7 May 1998 (1998-05-07) claims 1,8 ----	1,6-8
A	WO 97 34870 A (NEUROGEN CORPORATION) 25 September 1997 (1997-09-25) page 11 - page 12 -----	1,6,7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01799

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 9
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

I. Information on patent family members

International Application No

PCT/GB 99/01799

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
GB 1150397	A	30-04-1969	NONE		
WO 9818792	A	07-05-1998	AU	4787797 A	22-05-1998
			EP	0937072 A	25-08-1999
WO 9734870	A	25-09-1997	AU	2218997 A	10-10-1997
			EP	0888300 A	07-01-1999